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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	PAPER NUMBER
1653	10

DATE MAILED: 06/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/664,326	Applicant(s) HABERMANN ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9-18-00* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of April 26, 2002 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that examining Groups I-III would not constitute a serious burden. This is not found persuasive because having shown that these inventions are distinct for the reasons given in the previous office Action (Paper No. 6) and have acquired a separate status in the art as shown by their different classification (see p. 2 of Paper No. 6) and recognized divergent subject matter as defined by MPEP § 808.02, the Examiner has shown a serious burden of search (see MPEP § 803). Therefore, the initial requirement of restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

The Information Disclosure Statement filed March 30, 2001 has been considered. References EP 0 324 712 and EP 0 448 093 are not in English and do not have a translation. However, these references have been considered as to the information in U.S. Patent Nos: 5, 180,668 and 5,919,895, respectively, which Applicants indicate are the English language Equivalents (p. 1 of Paper No. 4).

Specification

The Specification is objected to for lacking a Brief Description of the Drawing. Correction is required.

Drawing

The drawing filed September 18, 2000 has been approved by the draftsperson.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 7 are unclear as to what is considered a "suitable" signal peptide (in step (d) of Claim 6 and last line of Claim 7). For example, is a signal peptide "suitable" if any level of protein activity is found in the culture supernatant in step (b)? Or, is a "suitable" signal peptide one that results in greater (or lesser) protein activity in the culture supernatant greater than a particular control (e.g. a hirudin derivative without a signal peptide) or is it the signal peptide that provides the highest activity in step (b))? In addition, Step (b) of Claim 6 is unclear as to the nexus of the expression rate and the activity of the protein in the culture supernatant. Is the protein active with the secretory

signal attached or must the secretory signal be removed for activity? It is unclear whether the protein activity in the culture supernatant represents all of the protein that was secreted with or without signal peptide intact or only those proteins that were secreted and in which the signal peptide was removed. Claims 8 and 9 are also rejected since they depend from these indefinite claims and do not correct the deficiencies.

Claim 8 is unclear as to the meaning of "expression". It appears that the claim was meant to read "wherein secretion of the desired protein and said suitable peptide occurs with simultaneous elimination of said suitable signal peptide" rather than "expression of the desired protein...". The term "expression" refers to the production of a protein from a polynucleotide. Thus, a protein is "expressed" at the point the protein is produced (in the cytoplasm) and, in this case, before the protein would be transferred out of the cell. Since the signal peptide is required for secretion of the protein, it would not be desired that it was eliminated simultaneously with expression. Claim 9 is rejected because it is dependent from an indefinite claim and does not correct its deficiencies. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for selecting a suitable signal peptide

for secretory expression of hirudin or a hirudin derivative using the method steps of the claims, does not reasonably provide enablement for a process for selecting a suitable signal peptide for secretory expression of any desired protein using the method steps of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

It appears that undue experimentation would be required to determine whether a signal peptide selected as suitable for hirudin expression would be suitable for expression of other "desired proteins". Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of Claims: The Claims are drawn to methods of selecting a suitable signal peptide for secretory expression of any desired protein by expression of hirudin connected to various signal peptides and comparing the expression rates, represented by the hirudin antithrombotic activity in the culture supernatant, as an indicator of the suitability of the signal peptide.

Nature of the Invention: The nature of the invention requires that the results of finding a suitable signal peptide for hirudin would be predictive of the suitability of that signal peptide for any other desired protein.

Amount of direction/guidance and presence/absence of working examples: The present Specification describes a method of finding signal peptides for expression of hirudin. There are no examples of using a fusion of hirudin to various signal peptides to find a suitable signal peptide for any other proteins.

State of the Prior art, Relative Skill of those in the art, and Predictability/Unpredictability of the art: It appears that those of relative skill in the art and the state of the prior art recognize an inability to predict the secretion efficacy of a given signal sequence for a given peptide as evidenced by Wong et al. (U.S. Patent No. 5,652,139, 1997). Wong et al. report that in trying to find a suitable signal peptide for IGF-1 expression in E. coli, several signal sequences reported to effectively secrete E. coli and/or heterologous proteins were found to be unable to secrete mature IGF-1 (see Col. 5, lines 6-16). Thus, it appears that whether or not a signal peptide, determined to be "suitable" by the method of the present invention, would be suitable for desired proteins other than hirudin would be highly unpredictable.

Quantity of Experimentation: For the reasons described above, practicing the claimed method to determine the suitability of a signal peptide for secretory expression of desired proteins other than hirudin would require undue experimentation.

Amendment of Claim 6 substituting "hirudin" for "a desired protein" in lines 1-2 (incorporation of the limitations of Claim 9 into the independent claim) would overcome this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Achstetter et al. (Gene (1992) 110: 25-31) in view of Schmid et al. EP 0 448 093 (1990; cited in IDS of Paper No. 4).

The examiner notes that U.S. Patent No. 5,919,895 ('895 patent) has been used as the English language equivalent of EP 0 448 093. Therefore, references to Schmid et al. will refer to the '895 patent.

Achstetter et al. disclose a method of selecting a signal peptide for secretory expression of hirudin or a hirudin derivative (p. 26, Col. 1, lines 27-30) comprising (a) expressing in a culture medium, hirudin having antithrombotic activity, and which has a defined amino acid, aa_x, at its N terminus, wherein said amino acid aa_x, is connected via its N-terminal to a signal peptide to be tested; (b) determining the expression rate by measuring protein activity in the culture supernatant; (c) repeating steps (a) and (b) with various signal peptides; and (d) selecting the suitable signal peptide by comparing the expression rates represented by the hirudin antithrombotic activity found in step (b). It is noted that Claim 6 does not provide any reference sequence to determine whether the "defined amino acid, aa_x" is an extra amino acid in addition to the 65 or 66 amino acids of the native hirudin sequence or if it is just the N-terminal amino acid of hirudin. Native hirudin contains either 65 or 66 amino acids and a hirudin derivative could contain any number of amino acids. Therefore, the limitation "which has a defined amino acid, aa_x, at its N-terminus, wherein said amino acid, aa_x is connected via its N-terminal to a signal peptide" is considered to encompass any signal peptide-hirudin protein wherein the signal peptide is at the N-terminus. Thus, the hirudin protein described in the method of Achstetter et al. is considered to have a defined amino acid, aa_x, at its N-terminus, wherein said amino acid aa_x is connected via its N-terminal to a signal peptide to be tested.

Achstetter et al. teach that the selection method involves expression in yeast and do not teach that the method involves expression in *E. coli*.

Schmid et al. teach that the expression of hirudin in *E. coli* would be advantageous over processes known in the art using yeast because "the cultivation of yeast cells takes longer and is more demanding than that of bacteria, for example, E. coli (Col. 2, lines 15-16). The bacteria, *E. coli*, appears to be preferred because of the availability of *E. coli* strains which show massive protein secretion into the culture medium (Col. 3, lines 32-34). Schmid et al. disclose a method of expressing Ala-hirudin derivatives in *E. coli* (Col. 6, lines 1-11) and suggest hirudin derivatives having any one of the amino acids Leu, Ile, Ala, Val, Gly, Ser, Asp, Glu, Asn, Gln, His, Met, Phe, and Tyr at the N-terminus wherein the amino acid is connected via its N-terminal to a signal peptide (Col. 2, lines 51-67). Schmid et al. state it is possible to obtain 2 g/L of a hirudin derivative with the N-terminal sequence of SEQ ID NO :1 (Ala-hirudin) in the culture supernatant of an E. coli secretor (Col. 3, lines 32-35).

Therefore, it would be obvious to one of ordinary skill in the art at the time of the invention, to practice the method of selecting signal peptides for the secretory expression of hirudin described in Achstetter et al. in E. coli using a aa_x-hirudin sequence as disclosed in Schmid et al. One of ordinary skill in the art would have been motivated to use E. coli in the method of selecting signal peptides because Schmid et al. state that the cultivation of yeast cells takes much longer and is more demanding than bacteria. Moreover, Schmid et al. shows that the method disclosed therein is highly successful in producing high concentrations of active Ala-hirudin (see Col. 3,

lines 24-26). Thus, it appears that the claims are unpatentable over Achstetter et al. in view of Schmid et al. for the reasons cited above.

Conclusions

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
June 26, 2002

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